



NEUROFILAMENTS AS A POTENTIAL BIOMARKER IN PATIENTS WITH MULTIPLE SCLEROSIS: A REVIEW OF LITERATURE

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ABSTRACT

Background: Multiple sclerosis (MS) is a chronic inflammatory neurodegenerative disease of the central nervous system (CNS) characterized by demyelination, axonal damage and loss of neurons. Its growing incidence has determined the need for more intensive research towards effective models for managing disease progression and evaluation of treatment response. Finding clinically relevant biomarkers has been a significant challenge.

Purpose: This review aims to summarize the findings from current relevant literature sources on neurofilaments as a potential biomarker of diagnostic and prognostic value in patients with MS.

Results: Recently, neurofilaments have been identified as the most promising and informative biomarkers of axonal damage and loss. Neurofilament concentration demonstrates a strong association with the disease course, activity and progression, disability accumulation and response to disease-modifying treatment. A significant correlation with future relapse rates, symptom worsening and risk of conversion from clinically isolated syndrome (CIS) to definite MS has also been established. Several MS therapies have demonstrated a substantial reduction in neurofilament levels upon treatment initiation.

Conclusion: The results available from real-world studies and clinical trials regarding neurofilaments as a reliable predictor and indicator of MS disease course are encouraging. They have consistently proven to be of utility if integrated into the diagnostic and therapeutic algorithm of MS patients. This review encompasses undeniable data confirming the considerable potential of neurofilaments for becoming the first globally verified biomarker for MS. The accessibility, safety, low cost and possibility for serial evaluation make the neurofilaments the perfect component to be implemented in routine clinical tests for MS.

Keywords: multiple sclerosis, biomarkers, neurofilaments, disease progression, disability, disease-modifying treatment,

BACKGROUND

Multiple sclerosis (MS) is a chronic inflammatory neurodegenerative disease of the central nervous system (CNS) characterized by demyelination, axonal damage and loss of neurons [1,2]. In the last decades, studies of MS immunopathology have grown remarkably. Our current knowledge of this mysterious disease is as great as it has never been before, and yet, it is still incredibly difficult to predict long-term clinical disease progression and prevent lasting disability.

Currently, modern diagnostic and prognostic strategies rest mainly on the clinical and neuroimaging features of MS patients [3]. Although the immunopathogenesis of MS is well-studied, there are still some crucial differences among individual patients with MS. The clinical course, progression and response to disease-modifying treatment (DMT) still vary widely among the MS population [4]. Some patients could stay relapse-free for years, also known as benign MS, and others would present with a very aggressive and rapidly progressing disease trajectory. It is still unclear what differentiates one group from the other and which factors impact the disease course exactly [5].

Current concepts indicate neurodegeneration and neuronal death as the main cause of disease progression and accumulation of disability. Nevertheless, axonal loss is an irreversible process, which highlights the imminent need for people with MS to be diagnosed as early as possible in the disease course [6]. The existing framework for the clinical management of MS patients relies predominantly on radiological markers (magnetic resonance imaging, MRI) and immunological evidence of inflammation (oligoclonal bands, OCBs). As essential as these tools are in MS diagnosis, they have not proven to be as useful and reliable in long-term monitoring and prediction of relapse rate, disease progression and treatment response [7]. Moreover, they have limited sensitivity when it comes to the so-called “smoldering” MS. Ultimately, the current knowledge emphasizes a growing need for alternative predictive biomarkers for monitoring and predicting disease progression that could potentially be integrated into the personalized approach to each MS patient [8].

REVIEW RESULTS

Neurofilaments: an overview

Neurofilaments (NF) are a type IV class of intermediate filaments specific to neurons. They are one of the major components of the neuronal cytoskeleton, maintaining its integrity, stability and regeneration [9]. They are found not only in the axons but also in the cell bodies, dendrites and synapses and are more highly concentrated in large myelinated axons. NF are classified into three groups depending on their relative apparent molecular masses on SDS-polyacrylamide gels: neurofilament heavy chain (NFH), neurofilament medium chain (NFM) and neurofilament light chain (NFL). While NFM and NFL levels are most elevated during acute axonal injury, NFH has demonstrated a substantial correlation with the process of chronic, irreversible neurodegeneration [10].

Several studies have confirmed serum NF (sNF) and cerebrospinal fluid NF (CSF NF) as biomarker showing the highest clinical correlation, and as such, NFL are more commonly evaluated [11] than NFM and NFH. Over the years, it has been established that the role of NF is crucial for the normal function of CNS, which has, in turn, focused the research interest to them as a potential biomarker of neuronal damage.

Normally, in healthy adult individuals, NF are constantly being released from the neurons, reflecting a normal process of aging. In a study conducted in 2020, Khalil et al. confirmed an age-related increase of NF [11] in individuals aged 60 and above and a close association of sNF with brain volume changes. This could be explained by subclinical comorbidities. However, during extensive axonal damage, NF are released in the extracellular space in much higher concentrations than normal, serving as direct real-time evidence of neuronal injury.

Several neurological disorders have been identified as precipitated by mutations in the NEFL gene, responsible for encoding NFL, such as certain types of Charcot-Marie-Tooth (CMT) disease and amyotrophic lateral sclerosis (ALS) [12, 13]. The significance of NFL in the process of neurodegeneration is further proven by their confirmed involvement in abnormal intraneuronal aggregates in Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), Huntington's disease (HD). Specifically in AD, there has been substantial evidence that sNF levels could be elevated 22 years prior to disease initiation [14].

Multiple sclerosis: challenges in the clinical practice

MS is the most common cause of disability among young, active people [6]. Its growing prevalence has warranted the need for more intensive research towards effective models for managing disease progression and assessment of DMT response. Although the main cause for the disease remains unclear, several environmental risk factors have been identified: vitamin D deficit, ultraviolet B (UVB) exposure, smoking, Epstein-Barr virus infection (EBV) [1,6]. Even so, not all aspects of MS could be explained by these underlying interrelations, implying the active involvement of others, possibly genetic etiological factors.

As apparently disease initiation is difficult to predict, it is extremely important for clinicians to have accessible and safe tools for taking control of the disease – proactive monitoring of the clinical course, treatment response and possible side effects in MS patients. Presently, the most routinely used clinical tool is MRI, in particular T2-weighted MRI, which visualizes lesions of demyelination in both white and gray matter [15]. Nonetheless, the correlation between the number, volume and activity of MRI lesions and the disability grade as measured by the Expanded Disability Status Scale (EDSS) [16] has been a subject of debate. Meta-analysis of the data investigating 1312 MS patients confirmed a modest correlation between the T2-lesions and age of disease onset, disease duration and course, disability, relapse rate, certain presenting symptoms, and gadolinium enhancement [17]. Many studies emphasize the controversial relevance of MRI activity in predicting the long-term prognosis and monitoring response to MS treatments.

The robust advances in MS pharmacology have led to a large variety of available drugs with distinct mechanisms of action, wide range of efficacy and risk of adverse events. The individual characteristics of each MS patient pose a challenge to clinicians in terms of constructing a therapeutic plan with optimal patient benefits and results. As of now, decision-making is based on analyzing multiple factors, including safety profile, expected adherence and individual preferences [18]. Regardless, each patient's response to DMT remains strictly individual, and the risk of serious adverse events persists. Currently, there is a lack of valuable clinical tools for the prediction of the treatment response and disease outcome.

Neurofilaments as biomarkers in MS

In recent studies, NF have been identified as a potential biomarker of axonal damage and loss [19]. Several aspects single them out as a promising and reliable biomarker in MS:

- They are accessible to be objectively measured and evaluated both in peripheral blood and CSF. NF levels in serum and CSF show a significant correlation. As the lumbar puncture is an invasive procedure and not appropriate for repetitive testing, NF measurement in serum would prove to be a worthy alternative.

- They are highly sensitive to the processes of acute and chronic axonal injury. Their concentrations demonstrate a definitive relation to periods of relapse and remission [20]. Furthermore, NF levels are significantly reduced during active MS therapies [21].

- Breakthrough technological advances have allowed for NF to be easily detected with simple, minimally invasive and highly sensitive methods, which suggests safe, periodic measurements. Commercial kits with different levels of sensitivity are available in all countries.

Neurofilaments in RRMS

RRMS is the most common pattern of MS. At the time of diagnosis, approximately 90% of patients are diagnosed with RRMS [22]. By definition, RRMS is characterized by distinct periods of new or worsening neurological symptoms (relapses), followed by periods of full

or partial recovery (remissions) [1, 22]. The term CIS defines a neurological event lasting for at least 24 hours, suggestive of demyelinating disease, but not yet meeting the criteria for dissemination in time [1]. All CIS events elevate the risk of conversion to a definite diagnosis of MS, although risk assessment is challenging and unpredictable in the individual MS patient.

Sensitive clinical tools for predicting the disease course in patients with CIS and newly diagnosed RRMS are intensively sought after. Convincing correlations have been confirmed between NF and the risk of conversion to MS after CIS. A multi-center study including 814 patients with CIS and RRMS among 22 independent study centers reported a substantial correlation between NF levels and the number of T2-lesions on MRI [23]. According to some authors, an increase in NF precedes structural abnormalities in the brain matter and may be indicative of a future relapse [24], thus influencing treatment decision-making.

It has been established that NF concentration reaches its highest peak 3-4 weeks after a relapse and remains elevated 6-12 weeks afterwards. Some authors even acknowledge CSF NF increase as the sole indicator of disease activity in patients with asymptomatic and oligosymptomatic MS and no lesion activity on MRI [25].

While studying a cohort of 85 patients with RRMS with follow-up for 2 years, investigators have reported that NF levels were associated with the presence of T1-gadolinium enhanced lesions. In addition, a decrease in NF was observed after the initiation of DMT [26]. For comparison, no correlation between serum CHI3L1 levels and any clinical or radiologic feature was identified in the same study.

In 2018, as part of an ongoing cohort study of 259 MS patients, Barro et al. confirmed NF as an independent indicator and predictor of EDSS worsening, the appearance of new or enlarging lesions on MRI, the pronouncement of brain volume loss and future relapse rate in patients with MS [18], which indicates NF as a significantly more comprehensive biomarker than MRI.

Neurofilaments in PMS

In contrast to RRMS, NF are far less extensively researched in patients with PMS. This probably stems from the fact that progression is still a complex concept that needs to be identified, assessed, and measured, and it evokes diagnostic uncertainty. PMS is a type of MS characterized by a gradual worsening of existing neurological symptoms with the accumulation of disability independent of relapses. It incorporates two MS phenotypes: secondary progressive MS (SPMS) and primary progressive MS (PPMS). Modern research data suggests that SPMS is not a separate disease entity but rather a stage in the natural evolution of the MS disease as a continuum. The estimated time before conversion from RRMS to SPMS is approximately 19 years [27].

To date, objective clinical or immunological markers of progression have not been implemented in the clinical practice yet. Thus, progression of the disease is usually registered retrospectively. Finding and identifying prognostic biomarkers for disease progression would be a

significant milestone in the clinical management of patients with PMS. Several studies have registered higher NF levels in PMS patients with disease activity than in PMS patients without disease activity. Correlations between NF and greater confirmed disability progression in PMS patients have been reported in the literature, including several major multi-center clinical trials (EXPAND and INFORMS). The ASCEND study of Natalizumab in SPMS confirmed that higher baseline NF was associated with greater brain atrophy at week 96. However, one study reported no significant association between NF and future disability in PMS [28]. In a meta-analysis of two randomized control trials, it has been determined that NF levels were associated with future disability regardless of the presence or absence of disease activity. Furthermore, NF were increased in those patients with objectively documented disability progression confirmed by a higher EDSS [29].

Neurofilaments and MS treatment

Recent success in pharmacological research has resulted in a myriad of disease-modifying treatments available for MS. The idea of highly effective therapy with fewer adverse events emphasizes the prospect of living life free of disability for MS patients [30]. Modern therapies have facilitated the concept of “freeing the patient from the disease” – the so-called no evidence of disease activity (NEDA) as an aspiration therapeutic goal in MS [31]. NEDA is defined as the lack of disease activity, disability progression and radiological activity (NEDA-3). Recently, a fourth component has been added – lack of brain atrophy (NEDA-4). Now more than ever, with intensively emerging DMTs reaching NEDA-4, it seems within reach for neurologists.

Current therapeutic approaches concentrate on the prevention of relapses, progression and accumulation of disability. Biologically, the therapy is aimed at battling the processes of inflammation and neurodegeneration. Limiting relapses in RRMS through effective DMT has shed light on the so-called “silent progression” as worsening independent of relapses through confirmed disability progression [32]. Those words discredit the concept of a patient being neurologically stable whilst not experiencing any relapses. In order to arrest the “smoldering” inflammation at the early stages of the disease and to avoid the accumulation of long-term disability, an urgent requirement for initiation of DMT as early as possible arises.

Despite the enlarging landscape of MS therapies, choosing the appropriate treatment for each individual patient remains difficult. As mentioned before, MS is an incredibly heterogenous disease with a variety of clinical subtypes, and the individual patient’s tolerance to DMT varies significantly. The most commonly used DMTs include beta-interferons, glatiramer acetate, ocrelizumab, natalizumab, rituximab, as well as newer drugs like teriflunomide, dimethyl fumarate, fingolimod, siponimod, ofatumumab.

Natalizumab is a humanized monoclonal antibody against the alpha chain of the VLA-4 integrin (CD49d) that inhibits cell migration towards CNS. It is a widely

used DMT in patients with RRMS and is particularly recommended in more aggressive clinical forms, that potentially reduces the annual rate of relapses and focal brain inflammation [33]. It has also been established as the drug with the highest risk of progressive multifocal encephalopathy (PML) caused by the John Cunningham virus (JCV). PML, although a rare event, is a considerable complication of natalizumab treatment and requires immediate treatment cessation. It has been suggested that NF may be an early predicting biomarker of PML, as reported by a study comprised of natalizumab-treated patients where NF were significantly higher at the PML-onset rather than in the pre-PML period [34]. A systemic analysis of several clinical trials among multiple patient groups demonstrated a significant reduction in NF in patients after initiation of natalizumab treatment, possibly due to the suppression of inflammatory activity by natalizumab, confirming NF as a potential biomarker of treatment efficacy [35]. An increase in NF has been linked to the recurrence of clinical and radiological disease activity after natalizumab treatment termination.

A decrease in mean NF level by 51% was observed in a cohort of PMS patients treated with *mitoxantrone* or *rituximab* [21] compared to the pre-treatment period. Furthermore, a reduction in NF was confirmed in patients with Gd-enhancing MRI lesions prior to baseline, reinstating NF as a biomarker of axonal damage and measuring treatment efficacy.

Siponimod is one of the more recently approved drugs for the treatment of SPMS. It is a next-generation selective sphingosine 1-phosphate receptor (S1PR) 1 and 5 modulator, reducing the risk of disability progression on EDSS with a generally well-tolerated safety profile [36]. In the EXPAND trial, Kuhle et al. confirmed that over a 21-month treatment period with Siponimod, the sNF were reduced only by 5.7%, whereas CSF NF were decreased by 10.5%. Meanwhile, an increase in NF levels was demonstrated in the placebo group.

Ofatumumab is one of the most prominent approved MS treatments available. It is a fully human anti-CD20 monoclonal antibody that has shown optimistic results in reducing the annualized relapse rate and MRI lesion activity in clinical trials. In the ASCLEPIOS I/II trial, ofatumumab has shown to increase the likelihood of achieving NEDA-3 in years 1 or 2 [37]. Consequently, lower NF levels were observed in all ofatumumab treated patients after therapy initiation, with the reduction being more significant in patients switching from teriflunomide to ofatumumab at week 12, confirming their prognostic value and role in monitoring the treatment response.

Neurofilaments: current limitations

In line with previous studies, it has been unequivocally

proven that sNF and CSF NF are significantly higher in MS patients compared with healthy controls. However, it is indisputable that an increase of NF is not equivalent to MS diagnosis. Moreover, NF are not specific to MS – as they reflect neuroaxonal damage and could be detected in other inflammatory and neurodegenerative disorders. Also, NF could not reliably identify the topography of the CNS lesions, an aspect that conventional MRI exceeds at. Besides, factors such as age, gender, body mass index (BMI), comorbidities also moderately influence NF concentration [24], therefore, at least an age-corrected NF range or index should be implemented for the purposes of future research. When it comes to MS, other components impact NF levels, such as disease activity and therapy usage, implying that appropriate individual ranges for MS subtypes should be developed. Ultimately, unification and standardization among different testing methods and laboratories is warranted for achieving the best results in routine clinical use. There are no clear criteria for what is to be considered normal or abnormal yet. Regarding MS, the general consensus seems to be leaning towards 400–1,000 ng/l for CSF NF and 3–30 ng/L for sNF [38]. All in all, NF should not be interpreted in a straightforward way but rather in the context of the individual clinical, biological and radiological features of each patient, integrated into a unique multivariate predictive model for every person with MS.

CONCLUSION

MS is a global problem, and its incidence is on the rise. The discovery of sensitive and reliable biomarkers to aid clinical judgement would be a revolution in MS management and treatment. At the moment, an “ideal” MS biomarker does not exist, and the search is set to continue. This literary review encompasses undeniable data that NF show substantial potential for becoming the first globally verified biomarker for MS. Its accessibility, safety, low cost and possibility for serial evaluation make it the perfect component to be implemented in a wider range of routine clinical tests. Its excellent ability to act as a predictor of MS worsening and as an indicator of treatment efficacy helps establish a more accurate prognosis. Certainly, studies are insufficient, and more data is needed as unanswered questions still exist. Nevertheless, the inclusion of NF in the diagnostic algorithm of MS could potentially fill some gaps in our understanding of this mysterious disease. Finally, it is our belief that by continued investigations of NF and their role we would further enrich the landscape for MS management as well as optimize the healthcare and quality of life of the individual MS patient.

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